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Natural Killer Cell-Derived Large Granular Lymphocyte Lymphoma of Lung Developed in a Patient With Hypersensitivity to Mosquito Bites and Reactivated Epstein-Barr Virus Infection

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A 17-year-old female developed natural killer (NK) cell-derived large granular lymphocyte (LGL) lymphoma of the lung. She had a past history of hypersensitivity to mosquito bites (HMB). After an eight-year chronic, active Epstein-Barr virus (EBV) infection, she developed multiple lung lesions and pleural effusion. In the effusion, 60% of the cells were LGL. They were CD2+, 3−, 16+, 56+, 57+, 45RO+/RA + weak, and possessed strong NK activity. No rearrangement of T-cell–receptor genes was detected. From all these results, a diagnosis of NK-LGL lymphoma of the lung was made. EB virus DNA was detected in cells infiltrating the pleural effusion. The clonality of the LGLs was determined by Southern blot hybridization with the terminal repeat sequence of EB virus as a probe, and by chromosomal abnormalities. The patient died from respiratory failure. Necropsy of the lung revealed diffuse lymphoma composed of polymorphic cells with typical angiocentric lesions. Reportedly, lymphomas of NK lineage show predominantly extranodal involvement, and primary lung lesions are rare. In the pleural effusion of the present case, abnormally high levels of soluble Fas ligand, interleukin-10 and interferon γ were detected. This hypercytokinemia, reflecting the microenvironment of lymphoma cells, may play a role in the progression of the lymphoma and organ injury in the lung. Am. J. Hematol. 59:309–315, 1998. © 1998 Wiley-Liss, Inc.

Key words: Epstein-Barr virus; pulmonary lymphoma; mosquito bites; natural killer; Fas ligand

INTRODUCTION

Mature human natural killer (NK) cells are distinguished by the following three features [1]: The first is large granular lymphocyte (LGL) morphology; the second is that they express cell surface CD56 and CD16, but do not express CD3 or TCR; and the third is major histocompatibility complex-unrestricted cytotoxic function,

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TABLE I. Temporal Change of Anti-Epstein–Barr Virus Antibodies in the Serum*

	1985/6	1986/2	1986/3 ↓[a]	1987/3 ↓[b]	1990/2	1990/10	1991/2	1991/7	1993/6
EB-VCA IgG	640	1,280	1,280	640	2,560	2,560	2,560	1,280	5,120
VCA IgM	<10	ND	10	<10	<10	40	40	20	80
VCA IgA	<10	ND	40	<10	20	40	40	10	<10
EA-DR IgG	<10	160	40	20	640	320	320	320	160
EA-DR IgA	<10	20	<10	<10	<10	<10	<10	<10	20
EBNA	40	40	20	40	40	20	20	10	40

*EB, Epstein-Barr; VCA, viral capsid antigen; Ig, immunoglobulin; ND, not done.
[a]Therapy with acyclovir (March–May, 1996)
[b]Therapy with IL-2, acyclovir, OK-432, and gIFN (March–July, 1987)

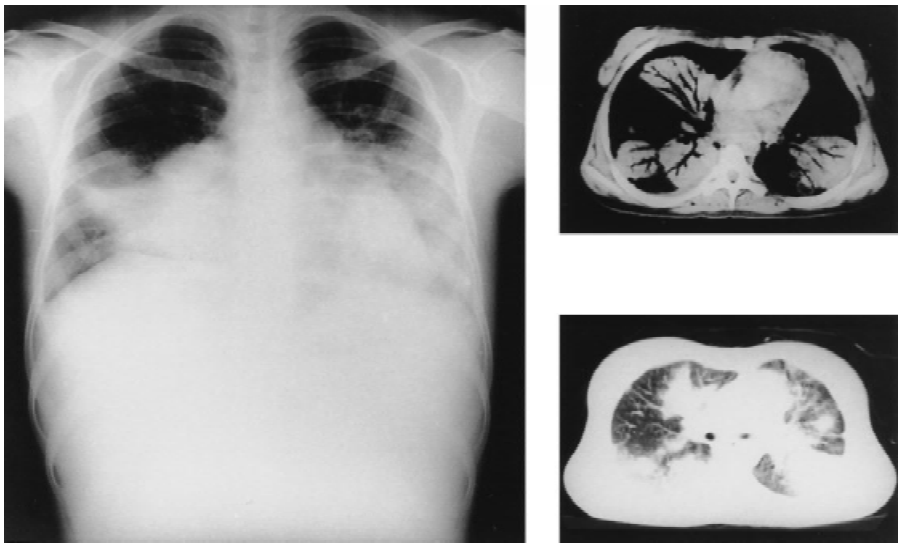

Fig. 1. PA-radiograph and computed tomography of chest showed multiple lesions in both lung fields.

that is, NK activity. Among the malignancies of NK cells, NK-LGL leukemia has been well characterized [2]. In contrast, the clinical, pathological, and immunological features of NK-LGL lymphoma have not been well studied. This might be due to difficulties of examining the above-mentioned three features of NK cells in lymphomas. However, since the late 1980s, it has been suggested that some cases of lymphoma are derived from NK cells, as judged by their phenotypical features, especially CD56 expression [3–5]. They constitute unique disease entity with extranodal involvement such as nasopharyngeal region, frequent infection with Epstein-Barr virus (EBV), and higher incidence in Orientals, Mexicans, and South Americans than Europeans and North Americans.

We report here a 17-year-old Japanese patient who developed EBV + NK-LGL lymphoma in the lung. Although lung involvement of suspected NK-cell–lineage malignancy has been reported in some cases, primary involvement is rare. As far as we know, only three such cases have been reported [6–8]. Our patient also had a history of hypersensitivity to mosquito bites (HMB) and suffered from chronic, active EBV infection (CAEBI).

We also examined the cytokines in the pleural fluid, which reflected the microenvironment of the lymphoma cells. We found evidence of overproduction of both Th1 and Th2 cytokines.

CASE REPORT

A 17-year-old female was referred to our hospital with dyspnea in June 1993. She had a past history of hypersensitive reactions to mosquito bites during her infancy. In 1985 (when she was nine years old), hepatosplenomegaly was noted. Judging from the typical profile of serum titer against EBV-specific antigens (1 × 160 anti-EA-DR immunoglobulin (Ig)G, 1 × 20 anti-EA–DR IgA), as shown in Table I, a clinical diagnosis of chronic, active EBV infection was made. In April 1993, multiple nodular lesions in both lung fields were unexpectedly found by chest roentgenogram. In May, dyspnea appeared due to increase of lung infiltration, as shown in Figure 1, and the patient consulted our hospital. She had hepatosplenomegaly due to chronic, active EBV infection, but no peripheral lymphadenopathy. Peripheral blood examination revealed a slight pancytopenia, white blood cell count of 3.5×10^9/l, hemoglobin of 10.9 g/dl, and platelets of 12.4×10^9/l, which was speculated to be due partly to hypersplenism, because differential counts

of white blood cells and examination of the bone marrow revealed no abnormalities. The biochemical profile revealed an elevated level of lactate dehydrogenase (LDH) (628 U/l). Immunological evaluation revealed the persistence of reactivated EBV infections (1 × 80 anti-viral capsid antigen [VCA] IgM, 1 × 100 anti-EA-DR IgG, 1 × 20 anti-EA-DR IgA as shown in Table I). The serum IgE level was 11,440 IU/ml. Her condition deteriorated and bilateral pleural effusion appeared in June. Based on the examination of pleural fluid, a clinical diagnosis of NK-LGL lymphoma was made. Combination chemotherapy was initiated, but the patient died of respiratory failure the next day. Permission for necropsy and informed consent for the following studies were obtained.

MATERIALS AND METHODS

Morphological Analysis

Peripheral blood smears and pleural effusion smears were stained with May-Gruenwald-Giemsa stain. The lung necropsy specimens were stained with hematoxylin-eosin stain.

Surface Marker Analysis

Peripheral blood cells or pleural effusion cells were washed twice with phosphate buffered saline (PBS) and diluted to the appropriate concentration. Cells were then reacted with monoclonal antibodies. The monoclonal antibodies used are listed in Table II. Leu-series antibodies were purchased from Becton-Dickinson (Bedford, MA). After red blood cells were hypotonically lysed, cells were washed and analyzed by FACScan. Immunohistochemical staining was performed on 4 μm-thick sections from formalin-fixed, paraffin-embedded blocks using the avidin biotin complex (ABC) method [10]. The antibody panel included anti-CD20 (Mx-PanB, Kyowa Medex, Tokyo, Japan), anti-CD45RA (MB-1, Bio-Science, Emmenbrücke, Switzerland), anti-CDw75 (LN1, Techniclone, Tustin, CA), anti-CD74 (LN2, Techniclone) for B-cell–related antigens, and anti-CD45RO (UCHL-1, Dakopatts, Copenhagen, Denmark), anti-CD43 (MT1, Bio-Science), and polyclonal anti-CD3ε (Dakopatts) for T-cell–related antigens.

NK Activity

Peripheral blood mononuclear cells (PBMCs) and pleural effusion cells were examined for NK activity by standard methods as previously described [10]. Briefly, effector cell suspensions were incubated with ^{51}Cr-labeled K562 target cells for 4 hr at 20:1 and 10:1 (E:T) ratios, and ^{51}Cr released into the supernatant was measured with a gamma counter. Percent specific ^{51}Cr release was calculated according to the formula reported [10]. We used freshly isolated PBMCs from normal volunteers as controls, and freshly isolated PBMCs from the patient were also prepared. Pleural effusion cells were suspended in 10% (vol/vol) dimethyl sulfoxide (DMSO) and frozen in liquid nitrogen until use. As pleural effusion cells comprised 60% NK cells and 30% T cells, T cells were depleted from thawed pleural effusion cells by the immunomagnetic-beads method with OKT3 (kindly provided by Dr. Y. Dohi, Osaka University) and Dynabeads M-450 sheep anti-mouse IgG (DYNAL, Oslo, Norway). With this method, CD3 + cells were reduced to 10% and LGL were enriched to 90% in the pleural effusion cell sample. We examined the NK activity of this enriched sample.

TABLE II. Characterization of Lymphoma Cells in Pleural Effusion*

a) Surface markers

CD	mAb	Reactivity %
CD2	Leu-5b	97.3
CD3	Leu-4	35.9
CD4	Leu-3a	32.1
CD8	Leu-2a	10.2
CD16	Leu-11c	61.2
CD56	Leu-19	66.4
CD57	Leu-7	18.3
CD11b	Leu-15	32
CD45RA	Leu-18	49.7
CD45RO	UCHL-1	93.2

b) NK activity of pleural effusion LGL cells

	% Killing activity (mean ± SD)	
Effector:target	LGL cells[a]	Normal control[b]
20	96.8 ± 2.3	(39.9 ± 14.9)
10	92.6 ± 6.9	(27.7 ± 12.2)

c) Chromosome abnormality
46XX, dup(1)(q25q32), 13p+:13/20
46XX, dup(1)(q25q32), inv(6)(p25q22), 13p+:7/20

*LGL, large granular lymphocyte; SD, standard deviation.
[a]LGL cells were enriched by the immunomagnetic depletion of CD3+T cells.
[b]Peripheral blood mononuclear cells of the healthy individuals (n = 59).

DNA Analysis

Genomic DNA was extracted from pleural effusion cells using standard methods. Purified DNA (10 μg) was digested with restriction endonucleases according to the manufacturer's instructions, subjected to electrophoresis on an 0.8% agarose gel, and transferred to Hybond N+ (Amersham, Buckinghamshire, UK) by alkaline transfer. Membranes were hybridized with ^{32}P-labeled probes that included the Cβ1 fragment of the T-cell receptor (TCR)-β gene, and the EBV DJhet fragment including termini sequence (kindly provided by Dr. E. Kieff, Har-

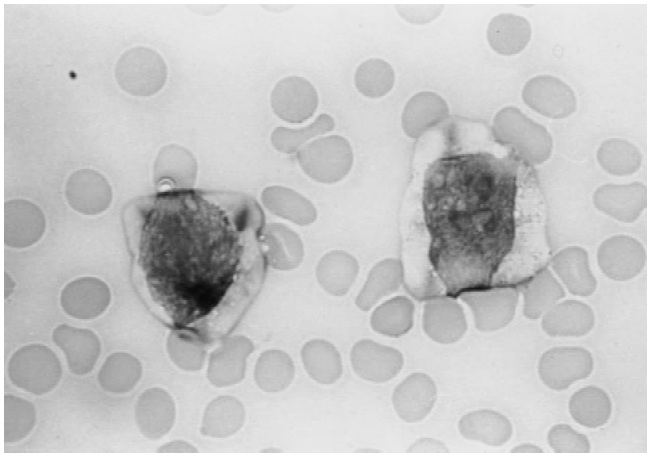

Fig. 2. May-Gruenwald-Giemsa staining of cells in pleural effusion showed that 69% of cells were large lymphoid cells with azurophilic granules.

vard Medical School). Polymerase chain reaction (PCR) analysis of EBV DNA was done with primers that generated a 429 bp fragment from the EBV BamHI W fragment, 5′-CCAGACAGCAGCCAATTGTC and 5′-GTGCCTTCTTAGGAGCTGTC. For positive controls for EBV DNA, we used the EBV + Burkitt lymphoma line, Raji, and the EBV + CD8 + T-LGL leukemia line, EBT-8 [11].

Chromosome Analysis

Cells in the pleural effusion were subjected to chromosome analysis, using the standard procedures. Metaphase spreads were G-banded and karyotypes were designated according to the International System for Human Cytogenetic Nomenclature (ISCN), 1991 [12].

Detection of Cytokines

The concentrations of interleukin (IL)-2, IL-4, IL-10, γIFN, IL-12, and soluble Fas ligand (sFasL) in serum and pleural effusion were examined using the enzyme-linked immunosorbent assay (ELISA) method as described elsewhere [13,14].

RESULTS

Cytological Analysis

May-Gruenwald-Giemsa staining of cells from the pleural effusion showed atypical, large lymphoid cells with moderately condensed chromatin, prominent nucleoli, and abundant pale blue cytoplasm with azurophilic granules (Fig. 2). These features were compatible with the morphology of LGL.

Surface Marker Analysis

Sixty percent of pleural effusion cells were CD2+, CD3−, CD16+, and CD56+. This phenotype was compatible with that of NK cells (Table II). By FACScan analysis, these cells with the NK phenotype showed relatively large forward scatter (FSC) compared with normal lymphocytes, which suggested that they corresponded to LGL. These LGL also reacted with anti-CD45RO as well as anti-CD45RA. Staining for CD45RO was bright, and 93.2% of cells were positive, whereas CD45RA staining was weakly positive. Therefore, these LGL were mainly CD45RO-positive, and some were RO/RA double positive. The residual cells were T cells, and there was no B-cell population. In the peripheral blood, there were few cells with NK markers (CD16+, 1.4%; CD56+, 6.6%; CD57+, 3.9%) and no atypical lymphoid cells.

Histology

Histology of the lung revealed slight fibrosis and necrotic changes in the subpleural space in which medium-to-large lymphoid cells showed a diffuse proliferation, principally in the alveolar walls, with accompanying small lymphocytes and macrophages (Fig. 3a). The infiltrating lymphoid cells had scanty cytoplasm and irregularly shaped nuclei, including occasional lobulated forms. Mitotic figures were infrequent. Immunohistochemical examinations showed that the atypical large cells were CD43+ and CD45RO+. CD3ε was intracytoplasmic positive. These cells infiltrated predominantly around the vessels, as shown in Figure 3b, which is compatible with angiocentric lymphoma. In contrast to the results with pleural-effusion–derived lymphoma cells, CD45RA (MB1)-positive cells were undetectable immunohistochemically in the lung, possibly due to weak expression. There were a few B cells that were positive for CD20, CD74, or CDw75.

NK Activity

As shown in Table II, purified LGL in the pleural effusion possessed extremely high NK activity, whereas NK activity of PBMCs was only slightly above zero (E:T 10, 8.5%; E:T 20, 9.5%).

DNA Analysis

Neoplastic cells showed no rearrangement of TCRβ (data not shown). These cells were shown by PCR analysis to be EBV positive (Fig. 4). By Southern blotting probed with the EBV terminal sequences, two clear bands, 9.8 and 3.8 kb, were detected (Fig. 4). These two bands indicated two clonal expansions of EBV-infected cells because single clonal expansions of EBV-infected cells show single bands, corresponding to a single pattern of fused terminal sequence existed in monoclonal circular episomal EBV DNA, as shown in Figure 4 for Raji and EBT-8. All these results indicated the clonal expansion of NK-LGLs in the pleural effusion of the patient. In contrast, PCR analysis showed no EBV genome in peripheral blood mononuclear cells.

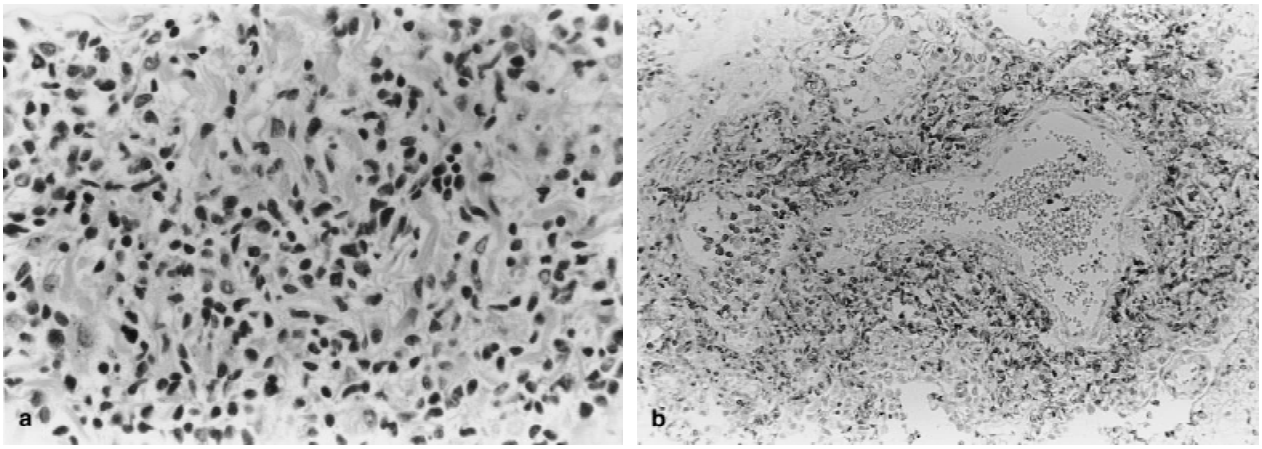

Fig. 3. Histology of lung necropsy. a. Hematoxylin-eosin stain; b. Immunohistochemistry of CD45RO. Medium-to-large lymphoid cells showed a diffuse proliferation principally in the alveolar walls, with accompanying small lymphocytes and macrophages. CD45RO-positive cells proliferated around the pulmonary artery.

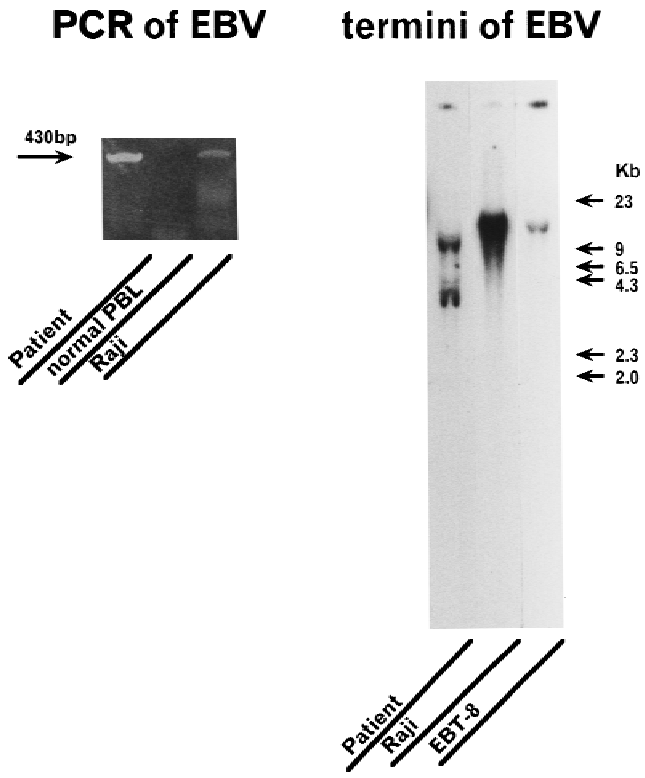

Fig. 4. Detection of EBV genome in pleural effusion cells. PCR amplification of EBV was done with primers from a region of the BamH1W fragment. DNA from Raji cells served as a positive control. Normal peripheral blood lymphocytes (PBL) DNA is a negative control under these amplification conditions. Termini of EBV were analyzed by Southern blotting. The patient's DNA sample from pleural effusion cells showed two clear bands, 9.8 kb and 3.8 kb. Raji and EBT-8 cell lines were used for positive controls indicating clonal integration of EBV.

Chromosome Analysis

Pleural effusion cells showed chromosomal abnormalities, as shown in Table II, which provided further evidence of the clonality of the LGL. The presence of two patterns of chromosomal abnormalities was consistent with the presence of the two bands containing EBV terminal sequence on Southern blots, again indicating that there were two different LGL clones.

Detection of Cytokines

Pleural effusion contained high concentrations of γIFN, IL-10, and sFasL (Table III), whereas serum showed no significant elevation of these cytokines. We also measured the level of IL-2 and IL-12, which are γIFN inducers, but they could not be detected in pleural effusion or serum. Although the serum concentration of IgE was high, IL-4 was detected neither in serum nor in pleural effusion.

DISCUSSION

There are at least three features that distinguish the NK-LGL lymphoma in this patient. The first is the mature-NK–cell origin of the lymphoma cells, and the primary lung involvement with angiocentric histology. The second is chronic, active EBV infection prior to the development of NK-LGL lymphoma. The third is cytokine elevation in the pleural effusion.

The evidence for the first feature is that the lymphoma cells of our patient fulfilled the three criteria of mature

TABLE III. Cytokines in Pleural Effusion and Serum*

Cytokine	Concentration		Detection limit
	Pleural effusion	Serum	
IL-2	<10 pg/ml	<10 pg/ml	10 pg/ml
IL-4	<0.3 pg/ml	<0.3 pg/ml	0.3 pg/ml
IL-10	670 pg/ml	36 pg/ml	5 pg/ml
IL-12	50 pg/ml	<50 pg/ml	50 pg/ml
γIFN	900 U/ml	<0.5 U/ml	0.5 U/ml
sFasL	4,833 pg/ml	<50 pg/ml	50 pg/ml

*IL, interleukin; IFN, interferon; sFasL, soluble Fas ligand.

NK cells [1], i.e., the morphology of LGL, the phenotype of CD2 + CD3 − CD16 + CD56+, and NK function. Moreover, no clonal TCR gene rearrangement was detected. Histologically, our case was characterized by polymorphic proliferation and angiocentric infiltration. These are compatible with the histological features seen in previously reported NK lymphoma or T/NK lymphoma [15]. Immunohistochemically, the lymphoma cells of our case were CD45RO+, CD43+, and cyCD3ε+, a pattern that has also been reported to be characteristic of T/NK lymphoma [15]. CD45RO expression is induced on normal peripheral blood NK cells by IL-2 activation [16]. Cytoplasmic CD3ε is expressed on both fetal NK cells and activated NK cells [17,18]. CD43 is also expressed on NK cells [19]. Therefore, expression of these T-cell–related markers is also consistent with NK lineage. Taken together with features of pleural effusion lymphoma cells and histological results, we diagnosed this case as NK-LGL lymphoma.

In the REAL classification, LGL leukemia and angiocentric lymphoma are classified as different entities [20]. We have previously reported that lethal midline granuloma of the nose, which is known to exhibit angiocentric features, is a neoplasm of LGL [21]. Thus, some cases of angiocentric lymphoma and NK/T lymphoma should perhaps be reclassified as NK-LGL lymphoma.

It has been reported that NK lymphoma shows predominant extranodal involvement, such as nasopharynx, skin, testis, soft tissue, gastrointestinal tract, and spleen [8,15]. In contrast to the upper respiratory tract involvement, lung involvement of NK lymphoma has rarely been reported [6–8], although some cases presented pulmonary extension in their terminal dissemination. On the other hand, the clinical entity of lung pulmonary lymphomatoid granulomatosis (LG) presents primary pulmonary lesions and exhibits angiocentric histology and EBV infection, as does lymphoma of NK-cell lineage, and indeed these two were formerly considered to constitute one disease [22]. However, Guinee et al. [23] reported that LG cases represented an EBV-positive B-cell proliferative disorder associated with an exuberant T-cell reaction. Ruling out pulmonary LG seems to be required for establishing a diagnosis of pulmonary NK-LGL lymphoma.

The second feature of our case is the complication of CAEBI. Prognosis of patients with CAEBI is poor; half of them show a fatal course [24]. Of special note, not a few cases were reported to develop EBV-related T/NK lineage malignancy. Children with CAEBI should be carefully followed for development of NK lymphoma in extranodal regions including the lung. In addition, our patient had a past history of HMB. According to Ishihara et al. [24], 31% of cases of CAEBI are complicated by HMB. The relationship between the immunological disturbance found in HMB, the mechanism of the inability to terminate EBV infection in CAEBI, and subsequent oncogenesis of NK-LGL lymphoma must be clarified in the future.

The last feature of our case was the cytokine profile in the pleural effusion. Besides overproduction of sFasL, the overproduction of both Th1 and Th2 cytokines, γIFN and IL-10, was found. One specific feature of the patient was that this overproduction was restricted to the pleural effusion, and was not found in the peripheral blood. The cytokine profile of the pleural effusion may reflect the microenvironment in the thorax where the lymphoma proliferated because the thorax is a closed space, in contrast to the peripheral bloodstream. Recently, we reported the same kind of cytokine overproduction in patients with hemophagocytic lymphohistiocytosis [13]. Reportedly, hemophagocytic syndrome is frequently accompanied by NK-lineage lymphoma [20]. There were no hemophagocytic lesions in the lung necropsy specimens of this patient, but the cytokine overproduction might have exacerbated the local organ damage of the patient. Controlling this cytokine overproduction with anti-cytokine antibodies may be helpful as a treatment modality to improve the prognosis and quality of life of patients with NK-LGL lymphoma.

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